Sex-Differences in Reproductive Hormones during Mini-Puberty in Infants with Normal and Disordered Sex Development

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Background

The early activation of the hypothalamic-pituitary-gonadal axis during infancy can be used in the evaluation of infants suspected of disorders of sex development (DSD). However, few data exists on sex-specific reference ranges for these hormones during early life

Thus, the aim was to evaluate sex-differences in reproductive hormone concentrations in serum from healthy infants in order to define sex-specific cut-off values and to apply these in infants with DSD.

Method

Design and setting: A cross-sectional study at a tertiary center for pediatric endocrinology at the University Hospital of Copenhagen.

Participants

- 1,840 healthy infants aged 2-5 months (1,041 boys, 799 girls)
- 27 DSD patients aged 2-5 months (Klinefelter syndrome: n=3, 45,X/46,XY mosaicism and male phenotype: n=8, Turner syndrome: n=4, complete androgen insensitivity syndrome: n=2)

Outcome measures: Serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol, sexhormone-binding globulin (SHBG), inhibin B, Anti-Müllerian hormone (AMH), dehydroepiandrosterone (DHEA), DHEA-sulphate (DHEAS), 17-hydroxyprogesterone (17-OHP), androstenedione, and LH/FSH-ratio.

Results

- LH and FSH concentrations showed overlap between sexes with LH being highest in boys and FSH being highest in girls (Fig. 1)
- The LH/FSH-ratio separated infant boys from girls with minimal overlap at a cut-off value of 0.32 (Fig. 1)
- Inhibin B and AMH concentrations were markedly higher in boys compared to girls, with minimal or no overlap, respectively (Fig. 2)
- In infants with Klinefelter syndrome, 45,X/46,XY mosaicism and male phenotype, and Turner syndrome, respectively, the LH/FSH-ratio matched the gender-of-rearing. However, infants with complete androgen insensitivity syndrome had LH/FSH-ratios within male range (Fig. 3).

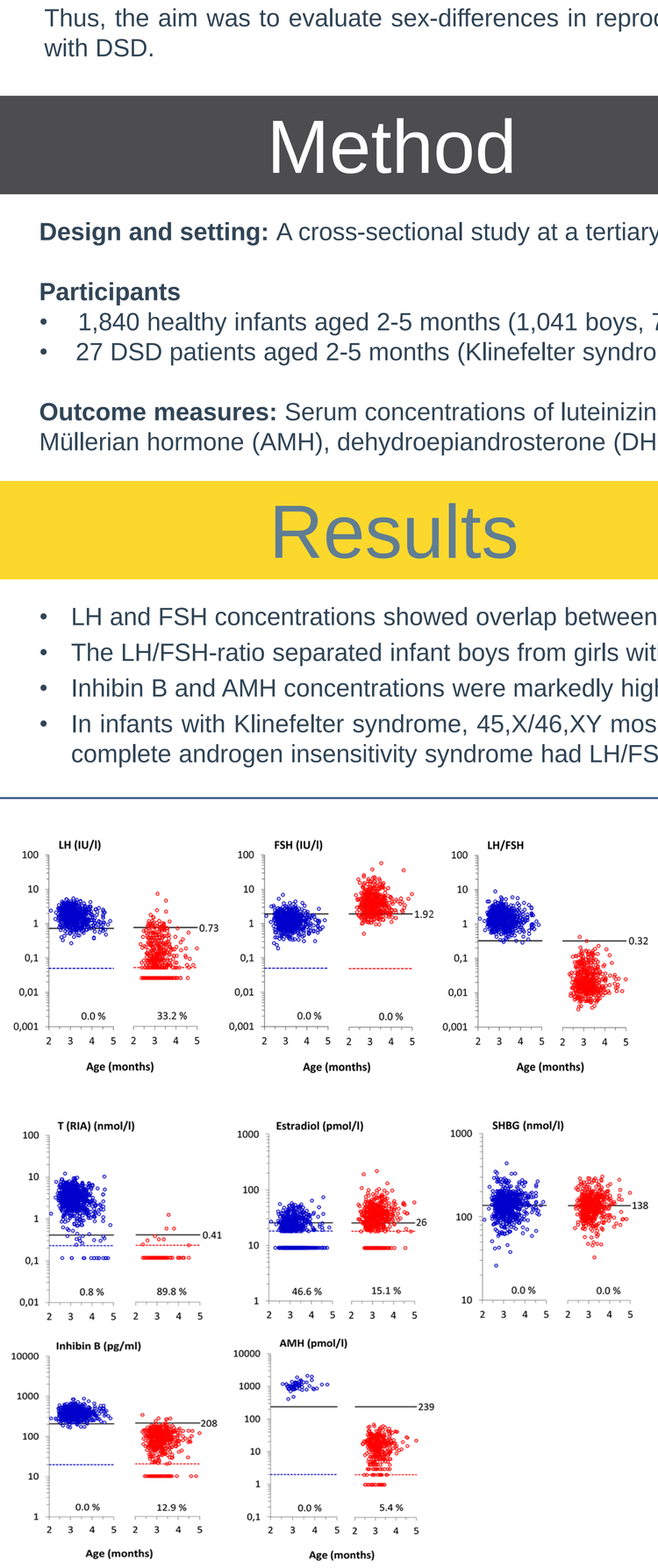

Figure 1
Serum concentrations of LH, FSH, LH/FSH-ratio, testosterone (radioimmunoassay [RIA]), estradiol, SHBG, inhibin B and AMH in boys (blue) and girls (red) during mini-puberty. The concentrations are shown on a log10-transformed y-axis (dotted lines: limit of detections [SHBG: not shown]; solid lines: cut-off value for separating boys from girls; %: percentage of measurements below limit of detection).

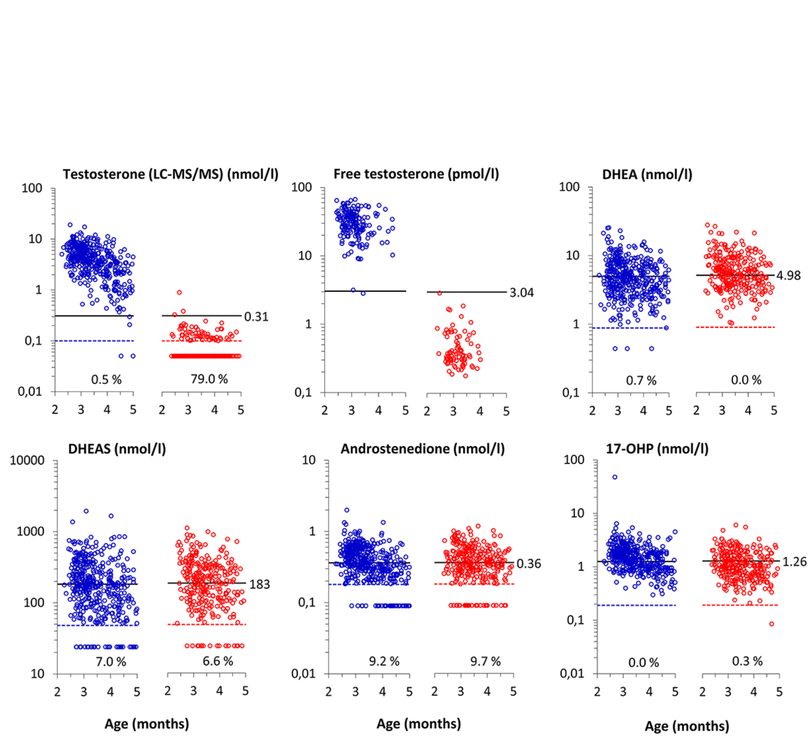

Figure 2
Serum concentrations of testosterone (LC-MS/MS) calculated free T (FT), DHEA, DHEAS, androstenedione and 17-OHP in boys (blue) and girls (red) during mini-puberty. *Further explanation to figure: please see text to Figure 1.*

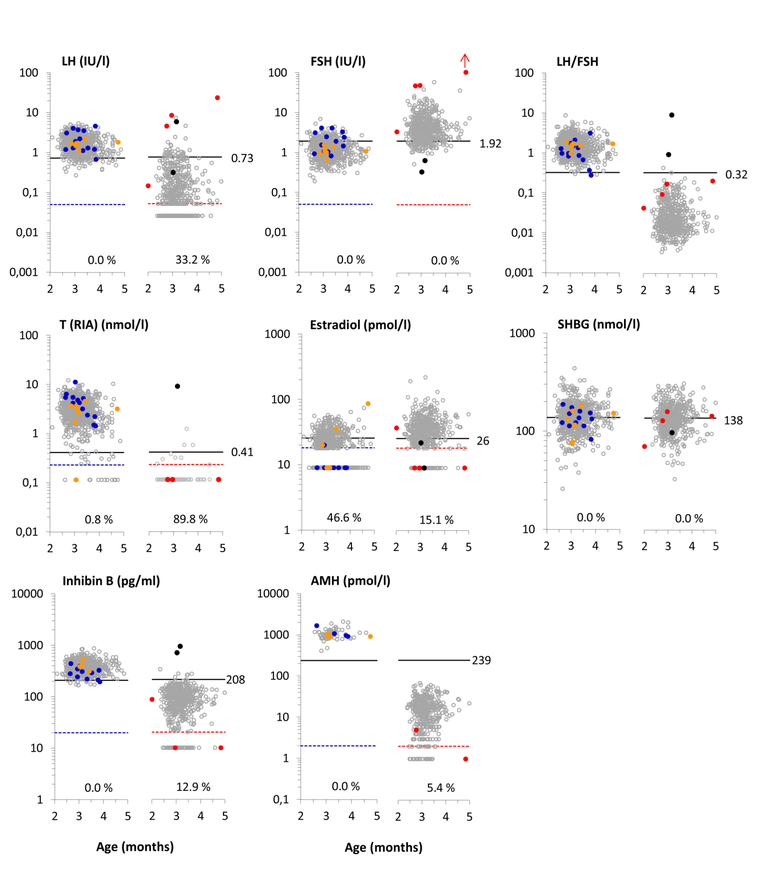

Figure 3
Serum concentrations of LH, FSH, the LH/FSH-ratio, testosterone (radioimmunoassay), estradiol, SHBG, inhibin B and AMH in patients with Klinefelter syndrome (blue), 45,X/46,XY mosaicism (orange), Turner syndrome (red) and complete androgen insensitivity syndrome (black) during mini-puberty compared to sex-specific reference ranges. *Further explanation to figure: please see text to Figure 1.*

Conclusion

- **AMH, inhibin B, testosterone and LH/FSH-ratio were superior in separating sex during mini-puberty**
- **Use of the LH/FSH-ratio may add valuable information in the work-up of infants suspected of DSD**

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